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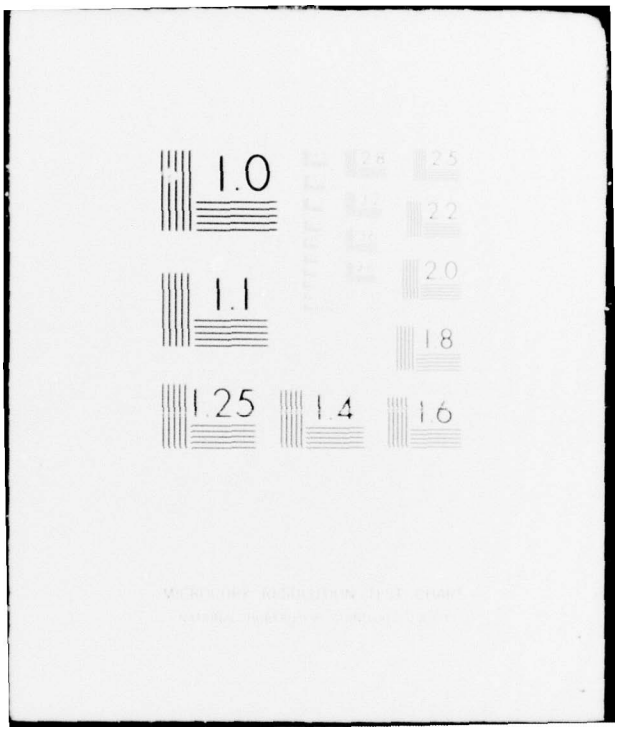
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THE EFFECTS OF ACUTE ALTERATIONS IN HEMODYNAMICS, OXYGEN AVAILABILITY AND ACID-BASE BALANCE ON THE PERMEABILITY OF THE GASTRIC MUCOSA.

ANNUAL PROGRESS REPORT
(FOR THE PERIOD 1 OCT. 76 TO 30 SEPT. 77)

DATE OF REPORT 1 Sept. 1977

BY

WALLACE P. RITCHIE, JR., M.D.

SUPPORTED BY
US ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
WASHINGTON, D.C. 20314

CONTRACT NO. DAMD 17-74-C-4014

UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE
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REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER	2. GOVT ACCESSION NO. / 3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle): The Effects of Acute Alterations in Hemodynamics, Oxygen Availability, and Acid-Base Balance in the Permeability of the Gastric Mucosa	5. TYPE OF REPORT & PERIOD COVERED: Annual Progress Report 1 Oct. 1976 - 30 Sept. 1977
	6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s): W. P. Ritchie, Jr., M. D.	8. CONTRACT OR GRANT NUMBER(s): DAMD 17-74-C-4014
9. PERFORMING ORGANIZATION NAME AND ADDRESS: University of Virginia School of Medicine Charlottesville, Virginia 22901	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: 61102A 3A161102B71R.01.073
11. CONTROLLING OFFICE NAME AND ADDRESS: US Army Medical Research and Development Command Washington, D. C. 20314	12. REPORT DATE: July 1977
	13. NUMBER OF PAGES: 8 pages
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)	15. SECURITY CLASS. (of this report): Unclassified
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Bile acid, hydrochloric acid, ischemia, gastric mucosal ulcerogenesis, methylprednisolone, metiamide.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Using a previously described model for acute gastric mucosal ulcerogenesis (Gastroent. 68:699, 1975), studies carried out during the period covered by the progress report indicated that methylprednisolone significantly protects against acute lesion formation by enhancing mucosal blood flow; that, at constant concentration of bile acid, lesion formation is a linear function of the concentration of hydrogen ion; and that, under non-ischemic conditions, in addition to affection significant inhibition of histamine stimulated H+ secretion, metiamide produces a concomitant reduction in venous "alkaline-tide".

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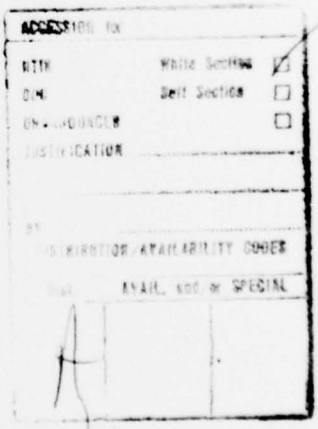
Finally, it was also shown that concomitant histamine infusion neither protects nor augments lesion formation under the experimental circumstances described.



PROGRESS REPORT: CONTRACT DAMD 17-74-C-4014

I. TITLE OF RESEARCH CONTRACT:

The Effects of Acute Alterations in Hemodynamics, Oxygen Availability, and Acid-Base Balance on the Permeability of the Gastric Mucosa.

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III. PERIOD COVERED: 1 October 1976 to 30 September 1977

IV. PROGRESS REPORT

(1) Methylprednisolone Protects Against Bile Acid Induced Acute Gastric Mucosal Ulcerogenesis. Although prophylactic systemic steroid administration has been reported to protect the gastric mucosa from acute ulceration under certain experimental conditions, the mechanisms of action involved are unclear. The present study investigated this phenomenon further in a proven model employing topical acid, topical bile acids in physiologic concentrations, and concomitant gastric mucosal ischemia (Gastroent. 68:699, 1975). Using vascularized, chambered ex-vivo wedges of proximal canine gastric wall, groups of animals (n=5-7ea.) were studied during 3 sequential 30 minute periods with the mucosa directly visualized. Group A= topical acid test solution alone (ATS=160mM HCl) during (1), (2), (3). Group B= (1) ATS, (2) ATS, (3) ATS+vasopressin (VP=0.01U/Kg-min delivered via the splenic artery). Group C= (1) ATS, (2) ATS+1mM Na Taurocholate (TC), (3) ATS+TC+VP. Group D= (1) ATS, (2) ATS+TC 30 minutes following a bolus IV injection of methylprednisolone, 30mgm/Kg (5), (3) ATS+TC+VP+S. Parameters evaluated= (1) net H+ flux, (2) aminopyrine clearance (AC), a measure of mucosal blood flow, (3) the degree of mucosal damage induced, the lesion index (LI), graded 0-5 by an independent observer. In non-ischemic mucosa, TC significantly increased ΔH+ and AC. S effected no further change. No lesions were observed. During period 3 (±SEM/30min):

	ATS	ATS+VP	ATS+TC+VP	ATS+TC+VP+S
ΔH+(μEq)	-109±34^{+}	-64±60^{+}	-439±49*	-517±83*
AC(ml/min)	1.69±0.16*	0.91±0.19	1.19±0.22	2.43±0.26^{*+}
LI(0-5)	0.33±0.33^{*+}	1.33±0.36^{+}	4.57±0.20*	2.20±0.49^{+}

*Sig. diff. vs. ATS+VP; +Sig. diff. vs. ATS+TC+VP

Thus, despite H+ "back-diffusion" comparable to ATS+TC+VP, methylprednisolone significantly protects against acute lesion formation by enhancing mucosal blood flow, a consequence of its alpha-antagonist-like properties.

(2) Influence of [H+] on Bile Acid Induced Acute Gastric Mucosal Ulcerogenesis. The combination of topical acid, topical bile acid, and concomitant gastric mucosal ischemia is acutely ulcerogenic (Gastroent. 68:699, 1975). Further, at constant [H+], the magnitude of mucosal damage is directly correlated (r=0.902) with increasing [bile acid] (Surgery 80: 98, 1976). The present study examined the influence of differing [H+] at constant [bile acid] on the same parameter. Methods- Using vascularized chambered ex-vivo wedges of proximal canine gastric wall, groups of animals (n=5-7ea.) were studied during 3 sequential 30 minute periods. Group A= (1) topical "neutral" test solution (160mM NaCl=NTS, pH 5.4±0.4), (2) NTS+1mM Na taurocholate (TC), (3) NTS+1TC+vasopressin (VP, 0.01U/Kg-min delivered via the splenic artery). Group B= (1) topical 100mM HCl-60mM NaCl "acid" test solution (100 ATS, pH 1.2±0.1), (2) 100 ATS+1TC, (3) 100 ATS+1TC+VP. Group C= (1) topical 160mM HCl (160 ATS, pH 0.9±0.1), (2) 160 ATS+1TC, (3) 160 ATS+1TC+VP. Indices evaluated= (1) net H+ flux (H+), (2) aminopyrine clearance (AC), a measure of mucosal blood flow, (3) potential difference (PD), (4) net TC flux (TC), and (5) lesion index (LI), graded 0-5 by an independent observer using photographs. Results= In non-ischemic mucosa exposed to TC, AC was significantly increased, ΔH+ ("back diffusion") increased as a linear function of [H+] (r=-0.772), and no lesions were observed. During VP administration (±SEM/30min):

	NTS+1TC+VP	100ATS+1TC+VP	160ATS+1TC+VP
ΔH+(μEq)	+38±28^{+}	-242±53*	-439±49^{*+}
AC(ml/min)	----	1.13±0.27	1.19±0.22
ΔTC(μM)	-0.6±0.6^{+}	-5±1*	-4±1*
LI(0-5)	0.2±0.1^{+}	2.2±0.3*	4.6±0.2^{*+}

*Sig. diff. vs. NTS+VP+TC; +Sig. diff. vs. 100ATS+TC+VP

Thus, at constant $[TC]$, (1) ΔH^+ ("back diffusion") increased as a linear function of $[H^+]$ (r=0.903); (2) as a consequence, lesion formation was also a linear function of $[H^+]$ (r=0.952); (3) mucosal absorption of TC was enhanced at low pH but bore no relation to the degree of mucosal damage induced.

(3) Influence of Intravenous Metiamide on the "Alkaline Tide". The H_2 antagonist, metiamide, has been shown to inhibit significantly gastric acid production, both in-vivo and in-vitro, in response to a variety of exogenous stimulants. One recent study, however, using in-vitro amphibian mucosa, suggests that, while metiamide inhibits H^+ secretion, mucosal metabolism, as indexed by total CO_2 production, proceeds at a rate comparable with non-inhibited tissue (Surg Forum 27:384, 1976). The present study was designed to reassess this finding in-vivo by measuring the "alkaline tide" during metiamide induced inhibition of histaminestimulated gastric acid production. Using vascularized chambered ex-vivo wedges of proximal canine gastric wall, 8 dogs were studied during 9 sequential 15 minute periods. During period 1-3, the mucosa of each was exposed to a topical acid test solution alone (ATS=100mM HCl, 60mM NaCl, 4G PEG, 5μCi ^{14}C-PEG); during periods 4-6, to topical ATS during concomitant intravenous infusion of histamine base (H), 1μg/Kg-min, and during periods 7-9, to ATS+H during intravenous infusion of metiamide (M) 10μg/Kg-min. During each period the following parameters of mucosal function were evaluated: (1) net H^+ flux, (2) the aminopyrine clearance, (AC), a measure of mucosal blood flow, and (3) systemic arterial and splenic venous pH, PO_2, PCO_2, Hct, and Hbg. Base deficit and HCO_3^- were determined using the Siggard-Anderson nomogram. Bicarbonate production was assessed by:

$$([HCO_3^-]_V - [HCO_3^-]_A) \times AC(ml/min)$$

The pertinent results (±SEM/15min):

	ΔH^+(μEq/15min)	AC(ml/min)	HCO_3^- OUTPUT(μM/15min)
Control	-41±16	0.96±0.11	19±3
Histamine	+294±42	1.61±0.15	80±16
Histamine + Metiamide	-16±27	0.91±0.08	39±5

These data indicate that, under the conditions of the present experiment, in addition to affecting significant inhibition of histamine stimulated H^+ secretion, metiamide produces a concomitant reduction in venous "alkaline tide", suggesting that its locus of action is proximal to the energy consuming, HCO_3^- producing step in active H^+ secretion.

(4) Influence of Histamine Induced H+ Secretion on Acute Gastric Mucosal Ulcerogenesis. It has been demonstrated in-vitro that burimamide-inhibited amphibian gastric mucosa is less resistant to bile salt induced damage, as judged by electrical indicies, than is spontaneously secreting mucosa (Gastroent, 71:760, 1976). The present study used ex-vivo vascularized chambered wedges of proximal canine mucosa to examine the converse: the potential protective effect of active H+ secretion induced by histamine on acute mucosal ulcerogenesis caused by the topical application of sodium taurocholate (TC) in acid solution and concomitant pharmacologic ischemia. Methods= Groups of dogs (n=5-6ea.) were studied during 3 consecutive 30 minute periods. Group A= topical acid test solution (ATS) during periods (1), (2), (3). Group B= (1) ATS, (2) ATS, (3) ATS+vasopressin (VP), 0.01U/Kg-min delivered via the splenic artery (which supplies the wedge). Group C= (1) ATS, (2) ATS+topical 1mM TC, (3) ATS+TC+VP. Group D= ATS+histamine (H), 1uGm/Kg-min IV, (2) ATS+H+TC, (3) ATS+H+TC+VP. Parameters evaluated during each period=net flux, aminopyrine clearance (AC), a measure of mucosal blood flow, and lesion index (LI), graded 0-5 by an independent observer using photographs. Results= In the absence of VP, TC significantly increased net H+ loss and AC relative to ATS; H resulted in significant H+ gain and further increased AC relative to ATS+TC; no lesions were noted under any circumstance. The results observed during period 3 (±SEM/30min):

	ATS	ATS+VP	ATS+TC+VP	ATS+H+TC+VP
ΔH+(μEq)	-109±43*	-108±60*	-359±66	-55±57*
AC(ml/min)	1.57±0.28	0.70±0.16*	1.10±0.09	1.37±0.43
LI(0-5)	0*	0.08±0.08*	2.20±0.26	1.60±0.51

*Sig. diff. vs. ATS+TC+VP

Thus, the combination of topical bile acid in acid solution and relative mucosal ischemia (compared to ATS+TC, where AC=3.36±0.69ml/min) is acutely ulcerogenic. Concomitant histamine infusion neither protects nor augments lesion formation under these experimental conditions.

5) Influence of Topical Prostaglandin E_2 on Acute Gastric Mucosal Ulcerogenesis. Due to the difficulty in obtaining adequate supplies of vasopressin, to date, only control data has been obtained in this particular study, using small doses of intraarterial vasopressin to induce acute mucosal lesion formation. The study is continuing.

(6) Patient Study. The cooperative study with the Burn Unit at the Brooke Army Hospital continues. Total bile acid content and concentration in the gastric aspirate of severely burned patients is being analyzed and correlated with the gastroscopic appearance of the mucosa on successive post-burn days.

V. PUBLICATIONS DURING THE CURRENT CONTRACT YEAR

Ritchie, W.P., Jr., Shearburn, E.W., III: Influence of isoproterenol and cholestyramine on acute gastric mucosal ulcerogenesis. Gastroenterology. In Press.

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Ritchie, W.P., Jr., Nading, A., Shearburn, E.W., III: Relationship of transmural electrical potential difference to changes in gastric mucosal permeability to H+ and blood flow. Am J Surg. In Press.

Cherry, K.J., Jr., Ritchie, W.P., Jr.: Methylprednisolone protects against bile acid induced acute gastric mucosal ulcerogenesis. *Surg Forum. In Press.*

Ritchie, W.P., Jr.: Acute post-traumatic hemorrhagic gastritis (Stress Ulcer): A continuing dielmma. Comprehensive Therapy 2:53, 1976.

Ritchie, W.P., Jr., Schneider, S., Shearburn, E.W., III: Mucosal ATP content during acute mucosal ulcerogenesis. Gastroenterology 72:1120, 1977.

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